Sustained DMARD-free remission in subgroups of patients with rheumatoid arthritis: an analysis of two prospective cohorts with early arthritis

Heutz, J.W.; Jong, P.H.P. de; Verstappen, M.; Mil, A.H.M.V.; Mulligen, E. van

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Judith W Heutz, Pascal H P de Jong, Marloes Verstappen, Annette H M van der Helm-van Mil, Elise van Mulligen**

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*Contributed equally

Department of Rheumatology, Erasmus Medical Center, Rotterdam, Netherlands (J W Heutz MD, P H P de Jong MD PhD, Prof A H M van der Helm-van Mil MD PhD, E van Mulligen PhD); **Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands** (M Verstappen MD PhD, Prof A H M van der Helm-van Mil, E van Mulligen)

Correspondence to: Dr Judith Heutz, Department of Rheumatology, Erasmus Medical Center, Rotterdam 3015GD, Netherlands
j.heutz@erasmusmc.nl

Summary

Background About 20% of patients with rheumatoid arthritis on disease-modifying antirheumatic drugs (DMARDs) can reach sustained DMARD-free remission. Nonetheless, the 2022 EULAR recommendations discourage complete cessation of DMARDs due to flare risk. The evidence behind this recommendation is obtained from trial populations using biological DMARDs, representing only a subgroup of the total population of patients with rheumatoid arthritis. We hypothesised that patients requiring biological DMARDs represent a subgroup that is less capable of reaching sustained DMARD-free remission compared with patients not requiring a biological DMARD.

Methods In this study we used data from two prospectively followed up populations of patients with early rheumatoid arthritis, the Leiden Early Arthritis Clinic (EAC) and the treatment in the Rotterdam Early Arthritis Cohort (tREACH), a treat-to-target steered trial in which biological DMARDs were started when patients had inadequate response to triple DMARD-therapy (methotrexate, sulfasalazine, and hydroxychloroquine). Patient partners were involved in the design of both the EAC and tREACH. The primary outcome was sustained DMARD-free remission, which was defined as absence of clinical synovitis after discontinuation of DMARDs for at least 1 year. Patients who did or did not receive biological DMARDs in 5 years (EAC) or 3 years (tREACH) were compared using Kaplan–Meier curves.

Findings 627 patients from the EAC were included, of whom 391 (62%) were female and 236 (38%) were male. The mean age was 60 years (SD 14) and 502 (95%) of 529 patients were White. 89 (14%) of 627 patients had ever used a biological DMARD and 538 (86%) had never used a biological DMARD. None of the patients that used a biological DMARD reached sustained DMARD-free remission, whereas 37% of the patients who never used a biological DMARD reached sustained DMARD-free remission at 5 years (hazard ratio [HR] 0·02, 95% CI 0·00–0·10; p<0·0001). From the tREACH population, 425 patients were included in the study. 286 (67%) patients were female, 139 (33%) were male, and the mean age was 54 years (SD 14); ethnicity data not recorded. 154 (36%) of 425 patients had ever used a biological DMARD and 271 (64%) had never used a biological DMARD during follow-up. None of the patients that used a biological DMARD reached sustained DMARD-free remission, whereas 15% of patients who never used a biological DMARD reached sustained DMARD-free remission at 3 years (HR 0·03, 95% CI 0·00–0·21; p<0·0001).

Interpretation For the subgroup of patients with rheumatoid arthritis who require biological DMARDs, sustained DMARD-free remission does not seem attainable. In contrast, in patients with rheumatoid arthritis who do not require biological DMARDs, DMARD-free remission is attainable. These data suggest that the current EULAR recommendation to not stop DMARD use might suffer from ascertainment bias. Future recommendations about DMARD cessation should be amended.

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Introduction

Sustained disease-modifying antirheumatic drug (DMARD)-free remission is one of the most desirable outcomes for patients with rheumatoid arthritis, since it is associated with sustained absence of symptoms and physical impairments.[1,2] DMARD-free remission seems the best proxy for cure both from rheumatologists' and patients' perspectives. In order to reach sustained DMARD-free remission, DMARD therapy needs to be tapered until all DMARDs are completely discontinued. The 2022 European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of rheumatoid arthritis advise against complete cessation of DMARDs after dose reduction or interval increase, due to a high risk of flares.[3] However, sustained DMARD-free remission is shown to be attainable and sustainable in about 20% of patients with rheumatoid arthritis.[1,2,4–6] Hence, there is an apparent disconnect between the recommendations from EULAR and the evidence from observationl studies and clincal trials, which was also summarised in a 2020 systematic literature review.[1]

Research in context

Evidence before this study

We searched PubMed from database inception to Jan 31, 2024, using the search terms "DMARD or drug-free remission" and "rheumatoid arthritis" for papers published in English. We found one systematic literature review summarising the evidence of (sustained) disease-modifying antirheumatic drug (DMARD)-free remission in patients with rheumatoid arthritis on DMARDs. This study showed that sustained DMARD-free remission can be reached in approximately 20% of patients. However, the 2022 European Alliance of Associations for Rheumatology (EULAR) recommendations discourage complete DMARD cessation in all patients with rheumatoid arthritis due to risk of flares. The evidence behind the EULAR recommendation is obtained from studies in subgroups of patients using biological DMARDs or in subgroups of patients positive for anti-citrullinated protein antibodies (ACPA) with high disease activity, however these subgroups only represent part of the total rheumatoid arthritis population.

Added value of this study

The results of this study suggest that the current EULAR recommendations might suffer from ascertainment bias since they do not seem applicable to the total rheumatoid arthritis population. We show that a subgroup of patients with rheumatoid arthritis with more severe disease characterised by biological DMARD use have a negligible chance of reaching sustained DMARD-free remission, whereas a subgroup of patients with rheumatoid arthritis not requiring a biological DMARD have a substantial chance of attaining sustained DMARD-free remission, especially if they are ACPA-negative. This is the first evidence of differences in attainment of sustained DMARD-free remission in subgroups of patients with rheumatoid arthritis, and could be a starting point for more research on DMARD tapering in subgroups of patients with rheumatoid arthritis in order to support personalised treatment strategies.

Implications of all the available evidence

This study might support future EULAR taskforces when the recommendations about DMARD cessation are updated. In addition, a 2024 analysis of 3-year data from the ARCTIC REWIND trial reported that 38% of patients using conventional synthetic DMARDs reached sustained DMARD-free remission, which could indicate that this population is more likely to reach sustained DMARD-free remission compared with patients using biological DMARDs.

As sustained DMARD-free remission is both attainable and desirable, we studied the literature supporting the EULAR recommendation (concerning the advice against complete DMARD cessation) in detail. The recommendation drew on three studies.[7–9] Two of these three studies looked at dose reduction or cessation of biological DMARDs.[7,9] Patients with rheumatoid arthritis using biological DMARDs are representative of only a part of the rheumatoid arthritis population since approximately 20–40% use a biological DMARD.[10] Both of these studies were done in a subgroup of patients with long-standing rheumatoid arthritis with inadequate responses to conventional synthetic DMARDs alone.[7,9] Of note, complete DMARD cessation did not occur in these trials. The third study reported a sustained DMARD-free remission rate of 17–25% depending on the study group.[8] This study was done in an early arthritis population with anti-citrullinated protein antibody (ACPA)-positive patients with very high disease activity included (mean swollen joint count 11·2) representing only a subgroup of patients with rheumatoid arthritis. Therefore, results from this study are not generalisable to the total rheumatoid arthritis population, especially since it is known that ACPA positivity is associated with a lower chance of attaining sustained DMARD-free remission.[11] The fact that the abovementioned studies in subgroups of patients with rheumatoid arthritis were used to formulate current recommendations that are meant for the total rheumatoid arthritis population might have led to ascertainment bias.

Thus, the EULAR recommendations appear to be based on studies in subgroups of patients with rheumatoid arthritis who are more likely to require biological DMARDs compared with the total rheumatoid arthritis population.[3,12] In addition, the recently published ARCTIC REWIND trial reported that 38% of patients using conventional synthetic DMARDs reached sustained DMARD-free remission, which could indicate that this population is more capable of reaching sustained DMARD-free remission compared with patients using biologicals.[13] Therefore, we hypothesised that the subgroup of patients who require a biological DMARD during the course of their disease (and thus do not respond to conventional synthetic DMARDs alone) are less likely to attain sustained DMARD cessation than patients who never need a biological DMARD. To test this hypothesis, we compared subgroups of patients with early rheumatoid arthritis with and without biological DMARD use for the outcome of reaching sustained DMARD-free remission over several years in two study populations.

Methods

Study design and participants

In this study we used data from patients with rheumatoid arthritis that fulfilled the 1987 American College of Rheumatology criteria, the 2010 American College of Rheumatology–EULAR criteria, or both, from two studies: the Leiden Early Arthritis Clinic (EAC) and the treatment in the Rotterdam Early Arthritis Cohort (tREACH) trial.

The EAC is a prospective population-based inception cohort from the Leiden University Medical Center, consisting of patients with recent-onset arthritis and a symptom duration of 2 years or less at time of inclusion. All patients in the EAC are treated in routine care and according to national and international guidelines for rheumatoid arthritis.[3] Promptly after diagnosis, conventional synthetic DMARDs are started with methotrexate being first choice. Another conventional synthetic DMARD is started or added when initial treatment is inadequate; a biological DMARD is considered when a patient with rheumatoid arthritis has an inadequate response to at least two conventional synthetic DMARDs. In the Leiden University Medical Center, the policy is to evaluate every indication for the start of biological DMARD in a weekly meeting in order to ascertain careful use of biological DMARDs. TNF inhibitors are the first choice for biological DMARDs; for a second biological DMARD the local preference is less strict, but frequently this involves a second TNF inhibitor. A more extensive description of the EAC can be found elsewhere.[14] All consecutive patients with rheumatoid arthritis included in the EAC from May 1, 2011, onwards were selected for the current study, as electronic prescription data on conventional synthetic and biological DMARDs became available from that date. Patients were not included if they had been enrolled in a clinical trial, or when no DMARD therapy was initiated.

tREACH is a multicentre, stratified, single-blinded trial that recruited patients between July 16, 2007, and June 25, 2013. Patients with inflammatory arthritis in at least one joint, a symptom duration of less than 1 year and age 18 years or older were included.[15] Patients were stratified into three groups according to their risk of progression to persistent arthritis, which was based on the prediction model of Visser and colleagues.[16] Based on the strata and randomisation, patients received one of the following initial treatment strategies: triple DMARD therapy (methotrexate, sulfasalazine, and hydroxychloroquine) plus glucocorticoids; methotrexate with or without glucocorticoid therapy; hydroxychloroquine; and glucocorticoids or non-steroidal anti-inflammatory drugs. The tREACH trial had a treat-to-target approach, aiming at low disease activity score (DAS <2·4). Treatment alterations could occur at each 3-monthly visit and treatment was intensified if DAS was 2·4 or greater. Intensification steps were as follows: (1) triple DMARD-therapy (methotrexate, sulfasalazine, and hydroxychloroquine); (2) methotrexate and etanercept; (3) methotrexate and adalimumab; and (4) methotrexate and abatacept. Medication was tapered if DAS was less than 1·6 at two consecutive visits. Medication was gradually discontinued, except for hydroxychloroquine and non-steroidal anti-inflammatory drugs, which were immediately stopped. In case of a flare (DAS ≥2·4) during tapering, treatment was restarted, according to the stage in the protocol. An extensive description of the study can be found elsewhere.[15]

From tREACH, all patients with rheumatoid arthritis who were treated with a DMARD or oral glucocorticoids were included in this study. Patients were not included when no DMARD or oral glucocorticoid treatment was initiated.

Patient partners were involved in the study design of the EAC, and subsequently informed of study results and follow-up investigations. Patient partners were also involved in the design and the development of the study protocol for the tREACH trial. For the specific research question addressed in this study there was no involvement of people with lived experience of arthritis.

The EAC was approved by the local medical ethics committee Leiden (B19.008). The tREACH trial was approved by the local medical ethics committee Rotterdam (MEC-2006-252). All patients gave written informed consent.

Procedures

In the EAC, research visits took place at baseline, at 4 months, and once a year thereafter. Independent of the scheduled visits, medical files of included patients were studied for occurrence of sustained DMARD-free remission during follow-up until May 31, 2022. Information on occurrence of sustained DMARD-free remission within 5 years of follow-up was used for this study. In the tREACH study, research visits took place at baseline and once every 3 months until 3 years of follow-up. Thereafter, visits were planned once a year until a maximum of 5 years. Based on the collected data at these visits, occurrence of sustained DMARD-free remission within 3 years of follow-up was determined. In tREACH, follow-up data from 3–5 years were not used for incidence of sustained DMARD-free remission, since frequent information on synovitis and DMARD use was not available after 3 years of follow-up. At each research visit in both the EAC and tREACH, information was collected by performing joint counts at physical examination, using questionnaires and by measuring serum autoantibody concentrations (at baseline), C-reactive protein, and erythrocyte sedimentation rate. Cutoff concentrations for autoantibody positivity were at least 7 U/mL for IgG-ACPA and at least 3·5 IU/mL for IgM-rheumatoid factor. Information on DMARD use was obtained from prescription data in the EAC and from electronic patient records in tREACH.

Outcomes

For this study, sustained DMARD-free remission was the primary outcome. In both the EAC and tREACH, sustained DMARD-free remission was defined as the absence of clinical synovitis (swollen joints at physical examination) after discontinuation of DMARD treatment (including oral glucocorticoids) for a minimum of 1 year.

During follow-up after sustained DMARD-free remission was reached, a late flare was defined as the reoccurrence of clinical synovitis or start of a DMARD (including oral glucocorticoids) after sustained DMARD-free remission (ie, >1 year after DMARD cessation).

As a secondary outcome we determined the length of follow-up (in years) in the EAC and tREACH, for all patients that reached sustained DMARD-free remission and maintained this sustained DMARD-free remission status during their entire follow-up period. This follow-up time was measured from the moment of DMARD cessation until the moment of the last visit or, for the EAC only, the time of medical file check.

Statistical analysis

The risks of sustained DMARD-free remission attainment over the course of 5 years in the EAC and 3 years in tREACH, were visualised using Kaplan–Meier curves comparing subgroups of patients with rheumatoid arthritis with and without biological DMARD use. The origin and start time of the survival curve was the date of the first visit. The end times were either attainment of sustained DMARD-free remission or the last observation in the study, or after 5 years (EAC) or 3 years (tREACH) of follow-up, when patients were censored. Cox proportional hazards models were used to compare survival distributions. Due to the occurrence of monotone likelihood or separation in our main analysis—caused by none of the patients using biological DMARDs reaching the outcome—we adopted Firth's penalised maximum likelihood bias reduction method for cox regression.[17] In addition, as sensitivity analysis, we corrected in the non-biological DMARD user group for the time until first biological DMARD prescription to account for immortal time-bias (event-free time) by removing patients who reached sustained DMARD-free remission before the median time to biological DMARD prescription from the analysis. In an additional sensitivity analysis ACPA-positive and ACPA-negative patients were studied separately. Baseline characteristics from patients with and without biological DMARD-use were compared using a Student's t-test (in case of normally distributed data), Wilcoxon rank-sum test (when normality of the data could not be assumed) or χ^2 test or Fishers' exact test (in case of proportions). In the tREACH study, at 3 years 63% of patients had missing data on sustained DMARD-free remission, of which 83% was due to loss to follow-up. Patients lost to follow-up per year are presented in a flowchart (appendix p 2). The percentage of missing data on sustained DMARD-free remission in the group of patients with and without biological DMARD-use were 68% and 60%, respectively. Baseline characteristics of patients with and without data on sustained DMARD-free remission at 3 years in the tREACH study, did not differ (appendix p 3). In the EAC, medical files of the selected patient population included between 2011

See Online for appendix

	EAC			tREACH		
	Biological DMARD ever (n=89)	Biological DMARD never (n=538)	p value	Biological DMARD ever (n=154)	Biological DMARD never (n=271)	p value
Age, years	54 (14)	61 (14)	<0·0001	53 (14)	55 (14)	0·15
Sex						
Female	57 (64%)	334 (62%)	..	120 (78%)	166 (61%)	..
Male	32 (36%)	204 (38%)	0·72	34 (22%)	105 (39%)	<0·0001
Ethnicity*						
White	63/67 (94%)	439/462 (95%)	1 (ref)	..	..	
Asian	..	9/462 (2%)	..	..	..	
Other	4/67 (6%)	14/462 (3%)	0·77	..	..	
Symptom duration, years	0·2 (0·1–0·8)	0·2 (0·1–0·5)	0·25	0·4 (0·3–0·6)	0·4 (0·2–0·6)	0·54
DAS44	3·5 (1·1)	3·3 (1·1)	0·034	3·7 (1·0)	3·1 (0·9)	<0·0001
SJC44	6 (3–10)	5 (2–10)	0·60	8 (4–12)	7 (4–11)	0·087
ACPA-positive	70/87 (80%)	232/536 (43%)	<0·0001	88 (57%)	132 (49%)	0·094
Rheumatoid factor-positive	63/84 (75%)	277/511 (54%)	<0·0001	80 (52%)	136 (50%)	0·12
CRP, mg/mL	11 (6–26)	10 (3–26)	0·21	9 (4–22)	7 (3–19)	0·22
ESR, mm/h	33 (22–45)	28 (11–43)	0·022	24 (14–44)	19 (11–36)	0·011
General health (VAS)	50 (20–70)	40 (20–60)	0·070	60 (47–70)	49 (27–64)	<0·0001
Pain (VAS)	70 (50–80)	60 (40–80)	0·0054	70 (40–80)	50 (30–70)	<0·0001
HAQ-DI	1·1 (0·8–1·8)	1·1 (0·5–1·5)	0·033	1·1 (0·8–1·6)	0·9 (0·4–1·4)	0·0001

Data are n (%), n/n (%), mean (SD), or median (IQR). ACPA=anti-citrullinated protein antibody. CRP=C-reactive protein. DAS44=Disease Activity Score based on 44 joints. DMARD=disease-modifying antirheumatic drug. EAC=the Leiden Early Arthritis Clinic. ESR=erythrocyte sedimentation rate. HAQ-DI=health assessment questionnaire disability index. SJC44=swollen joint count based on 44 joints. tREACH=treatment in the Rotterdam Early Arthritis Cohort. VAS=visual analogue scale. *In tREACH, data on ethnicity were not recorded.

Table: **Baseline characteristics of patients included from both populations**

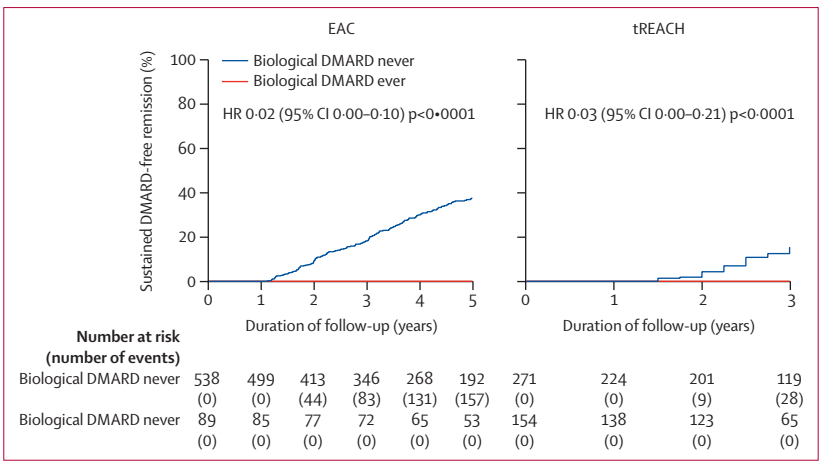

Figure 1: **Kaplan–Meier curves for attainment of sustained DMARD-free remission in the EAC and tREACH populations**

HRs are for biological DMARD users compared with biological DMARD non-users. DMARD=disease-modifying antirheumatic drug. EAC=the Leiden Early Arthritis Clinic. HR=hazard ratio. tREACH=treatment in the Rotterdam Early Arthritis Cohort.

and 2022 were individually studied for the outcome sustained DMARD-free remission. This means that for the current population, no missing data for the sustained DMARD-free remission outcome was present. All data were analysed with STATA (version 17), except for the penalised cox regression for which the coxpfh-package in R was used; p values of <0·05 were considered significant.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

In this study we used data from two prospectively followed up early rheumatoid arthritis populations, EAC and tREACH. From the EAC, 627 were patients were included; 391 (62%) were female, 236 (38%) were male, and the mean age was 60 years (SD 14); of 529 participants with available ethnicity data, 502 (95%) were White. 89 (14%) of 627 patients ever used a biological DMARD and 538 (86%) never used a biological DMARD during their follow-up period. At baseline, patients with biological DMARD use were younger compared with patients without biological DMARD use, had more active disease, with higher ESR and slightly worse scores on the health assessment questionnaire-disability index (table). In addition, they were more often positive for ACPA and for rheumatoid factor (table).

From tREACH, 425 patients were included in the study; 286 (67%) were female, 139 (33%) were male, and the mean age was 54 years (SD 14). Data on ethnicity were not recorded in the tREACH study. 154 (36%) of 425 patients ever used a biological DMARD and 271 (64%) never used a biological DMARD during 3 years of follow-up. At baseline, patients with biological DMARD use were more often female compared with patients without biological DMARD use, had a more active disease, with slightly higher ESR and HAQ-DI scores (table).

In the EAC population, none of the patients that used a biological DMARD during 5 years of follow-up reached sustained DMARD-free remission. On the contrary, for patients that never used a biological DMARD the risk of sustained DMARD-free remission was 37% (HR 0·02, 95% CI 0·00–0·10; p<0·0001; figure 1). In the tREACH population, none of the patients that used a biological DMARD during 3 years of follow-up reached sustained DMARD-free remission, whereas 15% of patients that never used a biological DMARD reached sustained DMARD-free remission (HR 0·03, 95% CI 0·00–0·21; p<0·0001; figure 1). When correcting for event-free time in the group that never used a biological DMARD by removing patients that reached sustained DMARD-free remission within the median time to first biological DMARD prescription in the EAC (2·09 years), 30% of patients that never used a biological DMARD reached sustained DMARD-free remission (appendix p 4; HR 0·02, 95% CI 0·00–0·14; p<0·0001). The results in the tREACH population remained unaffected by this since the median time to biological DMARD prescription in the tREACH population was 0·50 years. Moreover, similar results were obtained for males and females separately in both the EAC and tREACH populations (appendix p 5).

Since it is known that ACPA-negative patients have a better chance at reaching sustained DMARD-free remission, we additionally stratified our analysis for ACPA-status.[1,11] In the EAC population, ACPA-negative patients without biological DMARD use had a risk of 56% of reaching sustained DMARD-free remission after 5 years, compared with a risk of 14% for ACPA-positive patients without biological DMARD-use (HR 0·17, 95% CI 0·11–0·27, p<0·0001; figure 2). In the tREACH population, the risk of sustained DMARD-free remission after 3 years was 20% in ACPA-negative patients without biological DMARD use and 11% for ACPA-positive patients without biological DMARD-use (HR 0·49, 95% CI 0·23–1·07 p=0·073; figure 2).

The median follow-up time after DMARD cessation for all patients that reached sustained DMARD-free remission and maintained their DMARD-free remission status for the rest of their follow-up was 4·0 years (IQR 2·8–5·4) in the EAC population and 3·1 years (2·1–3·5) in the tREACH population (appendix p 6). Some patients reached sustained DMARD-free remission, although this was not sustained over their entire follow up due to late flares (>1 year after DMARD stop). Within the EAC population, 14 (9%) of 157 patients who reached sustained DMARD-free remission had a late flare. The median time to flare from DMARD cessation was 2·0 years (95% CI 1·4–3·0). In the tREACH population,

four (14%) of 28 patients that reached sustained DMARD-free remission flared during later follow-up. The median time to flare from DMARD cessation was 1·4 years (95% CI 1·25–2·25).

Discussion

To our knowledge, this study is the first to show in two independent populations with early rheumatoid arthritis that chances of reaching sustained DMARD-free remission are different for subgroups of patients requiring or not requiring biological DMARDs. This confirms our hypothesis that when patients require a biological DMARD, they are less likely to attain sustained DMARD cessation than patients who never require a biological DMARD. These findings could be explained by the reasoning that patients who need a biological DMARD (thus do not respond well to conventional synthetic DMARDs) have more severe disease and are therefore less likely to reach sustained DMARD-free remission. This was reflected in higher disease activity of biological DMARD users at baseline, and more patients who were ACPA-positive, both associated with lower chances of sustained DMARD-free remission.[1] Thus, biological DMARD use might be a proxy for severe rheumatoid arthritis, resulting in a negligible chance of sustained DMARD-free remission in these patients.[18] In addition, patients (and their physicians) on ongoing biological DMARD treatment might be hesitant to stop the treatment due to a risk of flares, which has been studied in the past.[19] As a consequence, discouragement of DMARD cessation for the total rheumatoid arthritis population based on only this subgroup of patients might not be valid.

One explanation for discouraging DMARD cessation in the EULAR recommendations could lie in the fact that evidence is derived from randomised controlled trials. Randomised controlled trials provide the highest level of evidence with the greatest internal validity. Unfortunately, sustained DMARD-free remission has barely been studied in randomised controlled trials including patients who only required conventional synthetic DMARDs. The ARCTIC REWIND trial by Kjørholt and colleagues showed sustained DMARD-free remission is feasible in 38% of patients on conventional synthetic DMARDs only.[20,21] Some other studies investigated withdrawal of conventional synthetic DMARDs, but only while continuing biological DMARDs.[22,23] One study investigated dose reduction but not complete cessation of conventional synthetic DMARDs and thus not sustained DMARD-free remission.[24] As a consequence, indirect evidence from randomised controlled trials was used for the EULAR recommendations on DMARD tapering. Due to specific inclusion criteria, this probably resulted in limited generalisability for the whole rheumatoid arthritis population, due to different patient characteristics.[25] For example, it was shown that a large proportion of patients with systemic sclerosis in the EUSTAR database would not be eligible for a range of different randomised controlled trials.[26] Thus, results from randomised controlled trials only apply to a proportion of the real-world disease population. When conclusions are subsequently translated to guidelines, this can lead to ascertainment bias. In this case, patients with rheumatoid arthritis that do not require biological DMARDs represent up to 70% of the rheumatoid arthritis population but are not represented in the trial evidence used for the current EULAR recommendation regarding DMARD cessation.

Observational studies have greater heterogeneity of patients, usually larger patient numbers and often longer follow-up. Use of the observational EAC favoured the follow-up time and rendered a large number of patients eligible for inclusion. Longer follow-up time is particularly beneficial when studying outcomes to prove that they are sustainable long-term, such as sustained DMARD-free remission.

Of note, proportions of biological DMARD-use in the EAC and tREACH were different. An explanation for this could be that treatment intensification procedures were different between the studies. The EAC is a cohort study in which biological DMARDs are prescribed in routine care, according to national guidelines. Also, every biological DMARD indication is evaluated in a weekly meeting with multiple rheumatologists. The tREACH study was a randomised controlled trial with a treat-to-target approach, in which treatment could be intensified every 3 months following a disease activity-based protocol. This probably provided an earlier opportunity for biological DMARD treatment than in routine care. Furthermore, in the tREACH protocol the opinion of the treating rheumatologist was not taken into account, whereas in

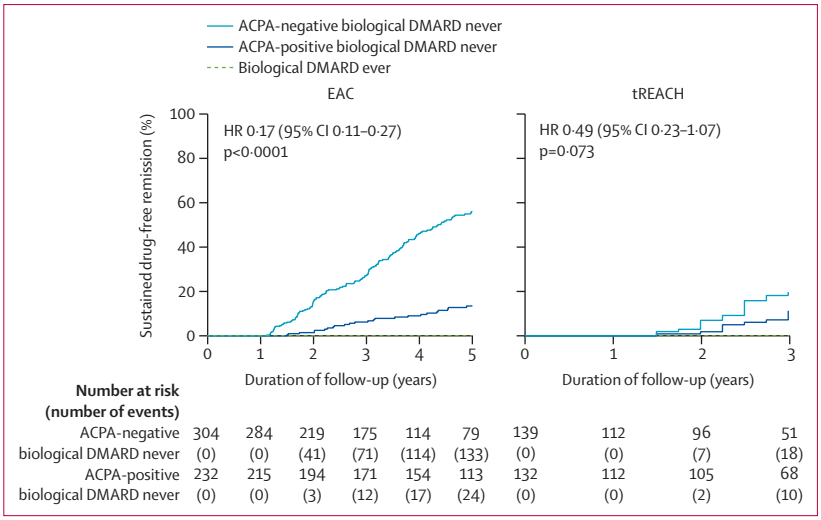

Figure 2: **Kaplan–Meier curves for attainment of sustained DMARD-free remission in patients that never used a biological DMARD by ACPA-status in the EAC and tREACH populations**

HRs are for ACPA-positive compared with ACPA-negative patients without biological DMARD use. Green lines are added for reference and indicate patients with a history of biological DMARD use. ACPA=anti-citrullinated protein antibody. DMARD=disease-modifying antirheumatic drug. EAC=the Leiden Early Arthritis Clinic. HR=hazard ratio. tREACH=treatment in the Rotterdam Early Arthritis Cohort.

routine care the patient's and rheumatologist's opinion might be a contributing factor. Consequently, patients in the two studies were similar, but not exactly the same.

Another difference was a shorter follow-up time in the tREACH. In general, patients using biological DMARDs require more time to reach remission compared with those using conventional synthetic DMARDs and subsequently taper and stop their DMARDs. This results in a delay for patients using a biological DMARD, which could lead to an underestimation of sustained DMARD-free remission when time is not unlimited. Because of differences in follow-up between the two studies, this delay could have led to underestimated sustained DMARD-free remission in the biological DMARD group within tREACH compared with the EAC population. Future research focusing on assessing patients reaching remission and eligible for tapering could shed light on how many patients might have the potential to reach sustained DMARD-free remission. In relation to this, our study could have suffered from immortal time bias, since the groups we compared (biological DMARD users *vs* non biological DMARD users) were defined during follow-up, and not at baseline. This might have led to an overestimation in the group that never used a biological DMARD, especially in the EAC where patients received biological DMARDs at a later timepoint compared with tREACH. A sensitivity analysis in which we removed patients that reached sustained DMARD-free remission within the median time to first biological DMARD prescription from the non-biological DMARD group, yielded similar results albeit with a slightly lower proportion of patients reaching sustained DMARD-free remission in the EAC. Nonetheless, results should be cautiously interpreted since an underestimation in the biological DMARD group and an overestimation in the non-biological DMARD group is still possible.

Contradictory to our findings, sustained DMARD-free remission attainment was previously reported in patients using biological DMARDs. Some of these studies were done in patients with established rheumatoid arthritis and long-term outcomes were not investigated; it was unknown whether DMARD-free status was maintained.[27,28] Others were trials in patients with early rheumatoid arthritis in whom initial therapy involved biological DMARDs.[4,5,29] In the EAC and tREACH, patients were treated according to a treat-to-target strategy starting wih conventional synthetic DMARDs. Biological DMARDs were only started after inadequate response to multiple conventional synthetic DMARDs; biological DMARD use was related to disease severity. Thus, results of this study are only applicable in settings with similar biological DMARD use. When biological DMARDs are, for example, part of first-line treatment, this would result in different chances at reaching sustained DMARD-free remission for patients using biological DMARDs.

The highest chance of sustained DMARD-free remission was observed in ACPA-negative patients (56%). This is in line with previous research showing that ACPA negativity is associated with greater chances at sustained DMARD-free remission.[11,12] Thus, ACPA-negative patients with early rheumatoid arthritis without need for biological DMARDs are the subgroup for which sustained DMARD-free remission is most achievable. Next to presence of ACPA, higher anti-modified protein antibody responses have been associated with risk of flares when tapering DMARDs.[30] Future studies could explore the additional contribution of the anti-modified protein antibody response to sustained DMARD-free remission attainment in rheumatoid arthritis.

Of all patients that reached sustained DMARD-free remission, approximately 90% did not flare during their follow-up. These patients maintained sustained DMARD-free remission over multiple years (median 3–4 years), after which their follow-up ended. This indicates that, although not observed, actual duration of sustained DMARD-free remission might have been even longer, implying that we might have underestimated this finding. Additionally, the few flares that occurred generally occurred in the first year after sustained DMARD-free remission was reached, indicating that chance of flare after several years is very low, as previously reported.[4]

A limitation of our study was that, although we adjusted for the most important confounder by stratifying for ACPA-status, we did not correct for other factors, such as disease acitivity, leading to possible residual confounding. However, the main difference between groups was disease activity which is connected to the exposure variable biological DMARD use, both can be seen as a proxy for more severe disease. Adjusting for disease activity would interfere with the effect of the exposure to the biological DMARD use on the outcome, therefore we chose not to correct for this. Since none of the biological DMARD users reached the outcome of sustained DMARD-free remission, sparse data bias is present in our dataset. However, we used penalised regression techniques to be able to obtain HRs and to reduce this bias. In addition, these HRs included relatively wide confidence intervals, due to the small effective sample size (ie, number of events). Finally, some patients were lost to follow-up in the tREACH after 3 years. Although characteristics of patients who were lost to follow-up and not lost to follow-up were similar, selection bias cannot be completely ruled out, since unobserved risk factors might still vary between groups. Strengths of our study include sample sizes and the combination of two study populations yielding similar results. In addition, we used a stringent definition for sustained DMARD-free remission, with absence of synovitis as an objective measure. Although sustained DMARD-free remission definitions vary widely between studies, we were able to apply a similar definition in both study populations.[1]

In conclusion, we show that for a subgroup of patients with early rheumatoid arthritis with more severe disease, characterised by biological DMARD use, reaching sustained DMARD-free remission is unlikely. In contrast,

in the larger subpopulation of patients with early rheumatoid arthritis not requiring biological DMARDs the likelihood of reaching sustained DMARD-free remission is substantially greater, especially when patients are ACPA-negative. Therefore, the EULAR recommendations on DMARD-cessation might suffer from ascertainment bias, since only part of the rheumatoid arthritis population was represented in the studies used to guide these recommendations. Future guidelines about DMARD cessation might therefore be amended.

Contributors

JWH, PHPdJ, AHMvdHvM, and EvM contributed to the conception and study design. JWH and EvM directly accessed, analysed, and verified the data. JWH wrote the first version of the manuscript and PHPdJ, MV, AHMvdHvM, and EvM revised it critically. AHMvdHvM and EvM supervised the study. All authors had full access to all the data in the study. All authors read and approved the manuscript and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

All data relevant to the study are included in the Article or the appendix. Additional data are available upon reasonable request to the corresponding author.

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